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Navoban® (tropisetron) alone and in combination with dexamethasone in the prevention of chemotherapy-induced nausea and vomiting: the Nordic experience

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To evaluate the efficacy and safety of Navoban® (tropisetron) three different Nordic multicentre trials were conducted during the period 1988–92. In all, 1050 patients were recruited from 15 centres. In the first study, Navoban® monotherapy was compared with a high-dose metoclopramide cocktail. In the second, Navoban® ± dexamethasone was evaluated for those patients not fully protected by Navoban® alone. In the third trial, Navoban® was evaluated for various chemotherapy regimens, for long-term efficacy, and for various risk groups of patients. Spontaneous intercycle variations were also evaluated. Navoban® was found to be as effective as the antiemetic cocktail but with a more favourable spectrum of side effects and a simpler schedule of administration. Navoban® was more effective during the acute than the delayed phase. Addition of dexamethasone significantly improved prevention of both acute and delayed emesis. Long term efficacy seemed to be stable up to 10 cycles of chemotherapy. Patients treated with non-cisplatin regimens showed significantly higher protection rates than patients treated with cisplatin. Various cancer diagnoses and cytostatic agents were also evaluated. Gender and age were important risk factors. Navoban® was found to be an efficacious antiemetic agent, especially regarding acute nausea and vomiting. Addition of a corticosteroid significantly improved the effect during highly emetogenic chemotherapy. The role of Navoban® for delayed emesis must be evaluated in future trials. The two most common side effects were headache and constipation. Overall, Navoban® was well tolerated and patient compliance with the drug was high.

Key words: Navoban® (tropisetron), corticosteroids, antiemetics, long-term effect, risk factors.

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Introduction

Blocking of the 5-HT_3-receptors in the proximal gastrointestinal tract, along the vagus nerve, and in the area postrema of the brain stem is an important measure to prevent chemotherapy-induced emesis.[1] Navoban® (tropisetron) is one of a family of highly specific antagonists to this subtype of serotonin receptors.[2] Thanks to the long terminal half-life of Navoban® in plasma (8 hours), its high specificity and affinity to the receptor and high bioavailability after peroral intake, and its simple once-a-day administration, it is possible to use it as an antiemetic agent. In the present paper, a number of pertinent questions regarding the efficacy and safety of Navoban® are addressed. Data from three different Nordic multicentre studies, encompassing more than 1000 patients treated during the period 1988–92, are presented to high-light important issues regarding Navoban® as an antiemetic agent. Comparison with a high-dose metoclopramide cocktail,[3] the value of adding a corticosteroid,[4] the long-term effect, naive vs. non-naive patients, the importance of various chemotherapy regimens, cancer diagnoses, gender, age and spontaneous effect variation between consecutive courses[5] are evaluated and discussed.

Materials and methods

During the years 1988–92, three different Nordic multicentre studies were conducted to evaluate the efficacy and safety of Navoban®. Navoban®, a highly specific 5-HT_3-receptor antagonist, was given i.v. or perorally with a once-daily schedule and a 5 mg

standard dose. It was given i.v. on Day 1 before the start of chemotherapy and then p.o. on Days 2–6. In the first study (ICS3516) Navoban® monotherapy was compared with a high-dose metoclopramide cocktail containing metoclopramide 3 mg/kg i.v., b.i.d., dexamethasone 20 mg i.v., and lorazepam 1 mg p.o., b.i.d. During the delayed phase, metoclopramide 10 mg p.o., t.i.d. was compared with Navoban® 5 mg p.o. Two hundred and fifty-nine evaluable patients with various cancer diagnoses were included in this open-label, randomised study (nine participating centres in Sweden, Finland, Denmark and Belgium). All patients were chemotherapy-naive and treated with cisplatin regimens. Two consecutive courses were evaluated. A quality of life questionnaire was also included in this trial. Nausea and vomiting were recorded separately during both the acute (Day 1) and the delayed (Days 2–6) period. In the second study (ICS 3525) Navoban® + dexamethasone was compared with Navoban® + placebo in the prevention of nausea and vomiting in women not fully protected by Navoban® monotherapy. The dexamethasone dose was 20 mg, i.v. on Day 1 and 4.5 mg b.i.d., p.o. on Days 2–6. The acute and delayed responses were studied. Two consecutive courses were followed (a screening and a test course). All patients (n = 160) were chemotherapy-naive and treated with cisplatin regimens for various gynaecological cancer diagnoses. Five departments of gynaecological oncology in Sweden and Finland recruited patients to this study. The third study (ICS 198) was an open, non-randomised, multicentre study with 15 participating Nordic (Swedish, Finnish and Danish) cancer centres. Both naive and non-naive patients (men and women) with various cancer diagnoses and various chemotherapy regimens (cisplatin and non-cisplatin) were included (n = 630). The patients were followed during as many cycles as possible (43 patients for 10 or more cycles). The aims of this study were to obtain new information on the efficacy and safety of Navoban® during long-term use, for naive and non-naive patients, for various chemotherapy regimens and cancer diagnoses, as well as vs. risk factors such as gender and age.

All three studies were approved by the local ethical committees of the participating centres and informed consent was received from all recruited patients.

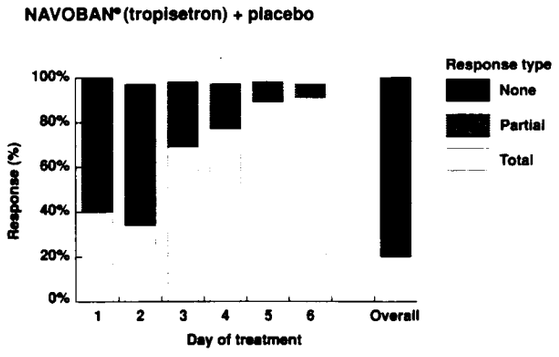
Results

In the open, randomised trial (n=259), Navoban® alone (63% complete protection) was as effective as a high-dose metoclopramide cocktail (64% complete protection) in prevention of acute vomiting (Table 1), but inferior in prevention of acute nausea (40% vs. 61% complete protection). During the delayed period (Days 2–6) no significant differences between the two treatment arms were recorded in the complete series. In a subgroup analysis of only ovarian carcinoma patients (n=66) from one trial centre Navoban® monotherapy seemed to be superior to low-dose metoclopramide in prevention of delayed nausea (Days 3–4). Regarding adverse events, headache, constipation and dizziness were more frequently recorded in the Navoban® group and diarrhoea, fatigue and extrapyramidal side effects (cumulative frequency 31%) more frequently in the cocktail group. An overall assessment revealed that Navoban® was better tolerated than the metoclopramide cocktail. The simple dosing (5 mg i.v. or p.o.) and schedule of administration (once a day) were also in favour of Navoban®.

In the double-blind, randomised study (n = 160), it was shown, in a group of women not fully protected by Navoban® monotherapy, that a combination of Navoban® and dexamethasone prevented acute vomiting in 75% of the cases compared with 40% for a combination of Navoban® and placebo ($p < 0.001$) (Figure 1). The corresponding figures for acute nausea were 75% and 37% respectively (Figure2). Delayed

Table 1. Frequency of patients with total, major, minor or no control of vomiting (treatment failure) in the first 24 hours of Courses 1 and 2 of chemotherapy

	Navoban® (tropisetron)	Antiemetic cocktail
Course 1		
No. of patients	131	128
Control of vomiting		
Total	83 (63%)	82 (64%)
Major	24 (18%)	18 (14%)
Minor	7 (6%)	11 (9%)
Treatment failure	17 (13%)	17 (13%)
95% CI		
Total (%)	[54,71]	[55,72]
Total or major (%)	[74,88]	[70,85]
Course 2		
No. of patients	120	112
Control of vomiting		
Total	56 (47%)	53 (47%)
Major	32 (27%)	26 (23%)
Minor	7 (6%)	15 (13%)
Treatment failure	25 (21%)	18 (16%)
95% CI		
Total (%)	[38,56]	[38,57]
Total or major (%)	[64,81]	[61,79]



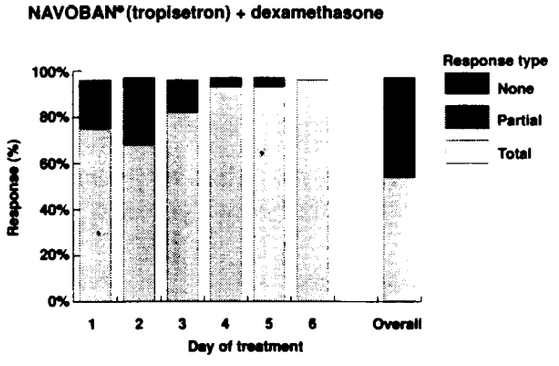
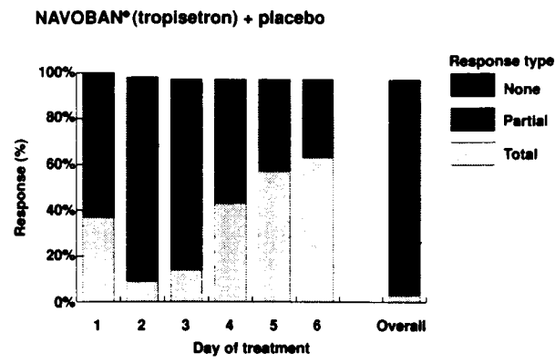


Figure 1. Prevention of vomiting during the test course (Course 2). Patients randomised to Navoban® plus placebo did significantly ($p = 0.007$) worse than those randomised to Navoban® plus dexamethasone.



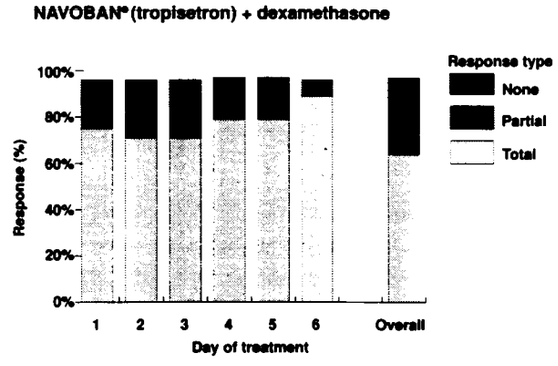


Figure 2. Prevention of nausea during the test course (Course 2). Patients randomised to Navoban® plus placebo did significantly ($p < 0.001$) worse than those randomised to Navoban® plus dexamethasone.

vomiting and nausea (Days 2–6) were also prevented at a significantly higher rate in the Navoban® dexamethasone group. There was a striking difference especially regarding the prevention of delayed nausea during Days 2–3 in favour of the corticosteroid-treated patients (Figure 2). Open-label rescue treatment improved the outcome during the acute phase, but the control rate dropped off rapidly during the delayed phase (Days 2–6) if the agents of the rescue therapy were administered only during the first 24 hours. Headache, the most common side effect of Navoban®, was less frequently recorded in the Navoban® dexamethasone group (11%) than in the Navoban® placebo group (34%). The same was true for constipation, with 14% vs. 20% in the two randomised arms. No serious adverse events were recorded in the corticosteroid-treated patients.

In the open-label, non-comparative, Nordic trial ($n = 630$) Navoban® ± rescue treatment was found to be effective during long-term fractionated chemotherapy (≥ 10 courses). Complete protection (60%–79%) and complete plus partial protection (93%–100%) remained constant over time (Figure 3). Protection from delayed nausea and vomiting (Days 2–6) also remained constant over time.

Rescue treatment (corticosteroid ± lorazepam), was allowed for treatment failures, and these cases were included in the long-term analysis. During repeated treatment with the same type of antiemetic regimen, a spontaneous variation in emetic control occurred with both improvement and deterioration (20%–30%). Complete protection (Day 1, Course 1) was achieved in 52% of cisplatin-treated patients and in 72% of patients not treated with cisplatin ($p < 0.001$). This difference was highly significant for both the acute and the delayed phases and also remained constant during consecutive courses. Emesis induced by streptozotocin and fotemustine, agents used in the treatment of endocrine tumours, was prevented most successfully by Navoban®. Dacarbazine (DTIC), known

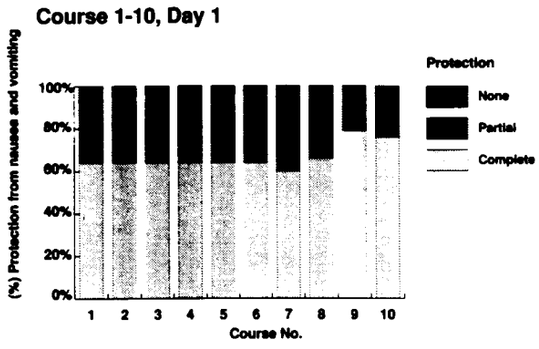


Figure 3. Acute antiemetic response (percentage) to Navoban® during 10 consecutive courses of treatment (the complete series).

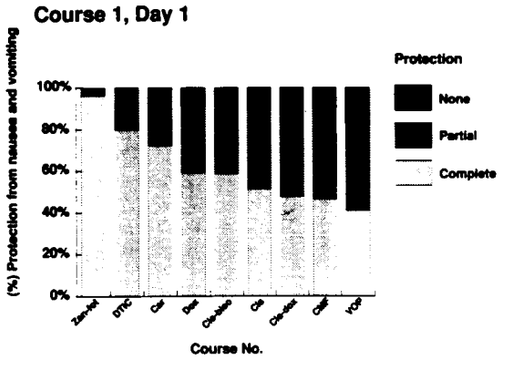


Figure 4. Antiemetic response during first day (acute phase) of Course 1 vs. type of chemotherapy. Zan-fot = streptozotocin–fotemustine; DTIC = dacarbazine; Car = carboplatin; Dox = doxorubicin; Cis-bleo = cisplatin–bleomycin; Cis = cisplatin; Cis-dox = cisplatin–doxorubicin; CMF = cyclophosphamide–methotrexate–fluorouracil; VOP = teniposid–vincristine–cisplatin.

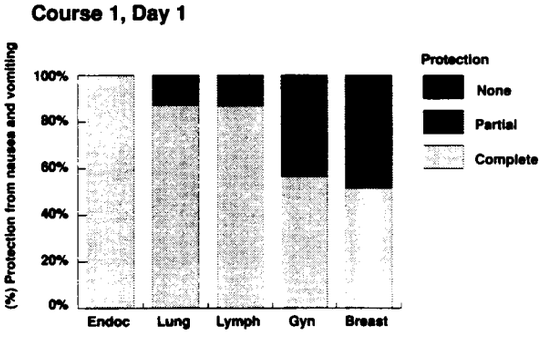


Figure 5. Control rates of acute nausea and vomiting during the first course of chemotherapy vs. five main cancer diagnoses (endocrine tumours of the gastrointestinal tract, lung cancer, lymphomas, gynaecological malignancies, and breast cancer).

to be a highly emetogenic drug, also responded well to Navoban®, with 80% complete protection from nausea and vomiting. Carboplatin came next, with 72% complete protection and only 5% with treatment failure. Patients treated with doxorubicin and combinations containing doxorubicin as the main emetogenic agent achieved complete prevention in 59%, which was not different from patients treated with cisplatin or cisplatin combinations (Figure 4). Women treated with a cisplatin–doxorubicin regimen for ovarian carcinoma, CMF for breast cancer and cisplatin–teniposid–vincristine for endometrial carcinoma, were at higher risk of incomplete antiemetic control (Figure 5). A spontaneous variation with regard to antiemetic outcome between the consecutive cycles were recorded. For patients with partial protection of acute nausea and vomiting in Course 1, 34% improved to complete protection and 10% deteriorated to no protection in Course 2 (Figure 6). Approximately the same variation was also noted for the control of delayed nausea and vomiting (recorded on Day 3 in Courses 1 and 2). A relationship was found between the degree of protection of acute nausea and vomiting and the grade of delayed nausea and vomiting. Despite complete control of acute emesis, 40% of the patients will still suffer from delayed emesis of various grades (Figure 7). The hypothesis that delayed emesis in fact is an early type of anticipatory emesis is not supported by these data; rather, they indicate that it has – at least partly – a different aetiology from acute emesis.

Discussion

Introduction of the 5-HT_3-receptor antagonists in the late 80s was an important improvement in antiemetic therapy. Antiemetic cocktails containing high-dose metoclopramide were then successively replaced by this new class of drugs. Regarding prevention of acute nausea and vomiting, the efficacy and safety of the 5-HT_3-receptor antagonists are undisputed. Navoban®, a highly specific 5-HT_3-receptor antagonist, was found to be of similar efficacy to a rather complicated high-dose metoclopramide cocktail, but with a more favourable spectrum of side effects and a much simpler and more convenient administration schedule.[3] Adding a corticosteroid improves the protective effect during both the acute and the delayed phases of chemotherapy-induced emesis. Patients not fully protected

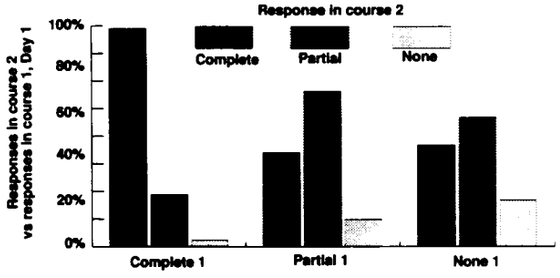


Figure 6. Antiemetic responses in Course 2 vs. responses in Course 1 (ICS 198, Nordic Study, complete series: $N = 630$).

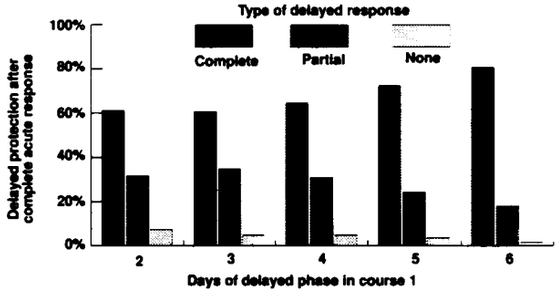


Figure 7. Type and frequency of delayed nausea and vomiting after complete protection during the acute phase (Day 1) of Course 1 (ICS 198, Nordic Study, complete series: $N = 630$).

by Navoban® monotherapy benefited significantly from addition of dexamethasone 20 mg i.v. during the acute phase and 9 mg daily during the delayed period. Delayed nausea was especially well controlled in 75%–80% of the cases with a combination of Navoban® and dexamethasone. A single corticosteroid dose given during the first 24 hours is not adequate to prevent delayed emesis during cisplatin chemotherapy. The frequency of the two most common side effects of Navoban®, headache and constipation, was lower in the corticosteroid group than in the placebo group. The reason for this difference is not known.[4] The role of the serotonin receptor antagonists *per se* during the delayed phase is still under discussion, and further randomised and comparative studies are needed to address this important topic. Corticosteroids have been found to be active as antiemetics, but their mechanism of action and the optimum dose are unknown.[6,7]

The antiemetic effect of Navoban® seems to remain constant over time if rescue treatment is allowed for treatment failures. However, analysis of the long-term effect is complicated by methodological problems. There were significant differences between patients treated with cisplatin and non-cisplatin regimens and this was true both for the acute and the delayed period and during long-term follow-up. Nausea and vomiting induced by streptozotocin, fotemustine,and dacarbazine are successfully prevented by Navoban®. Excellent results can also be achieved for carboplatin. Doxorubicin and cisplatin regimens used to treat breast cancer and gynaecological cancers still offer a certain problem regarding nausea and vomiting. Besides this, women and young patients are two groups especially at risk from less well controlled emesis during chemotherapy.[5] During fractionated chemotherapy, a spontaneous variation in antiemetic response can be anticipated between similar courses, despite identical antiemetic treatment. The variation is often 20%–30% with both improvement and worsening. Influencing factors other than the pharmacological ones are the probable explanation of these fluctuations in antiemetic effect.

Conclusion

In summary, Navoban® was found to be a highly effective, safe and simple-to-use antiemetic agent for both cisplatin and non-cisplatin-containing chemotherapy. The effect during the acute period is obvious, but during the delayed phase data are inadequate to define its final role as an antiemetic agent. However, in combination with a corticosteroid it works well, with complete protection from nausea and vomiting in 75%–80% of the cases treated with highly emetogenic cisplatin-containing chemotherapy. Long-term effect seems to be stable. There are sex and age differences in the antiemetic response. A spontaneous between-course variation of 20%–30% is anticipated during extended chemotherapy. A relationship between acute and delayed nausea is noted, but there is still room for partly different aetiological mechanisms for the two entities.

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